

A Within Subjects Comparison of Two Antegrade Flushing Regimes in Children

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This study was a part of a dissertation presented to the Graduate School of the University of Florida in partial fulfillment of the Doctor of Philosophy degree requirements.

Study design

This study compared two flushing regimens utilizing a cross-over design embedded in a single subject A-B-C-B'-C'-B1' design with subjects acting as their own control; thereby ensuring the highest possible degree of equivalence across treatment conditions and allowing greater precision and efficiency in estimates of treatment effects (Janosky, Leininger, Hoerger & Libkuman, 2009; Piantadosi, 2005; Portney & Watkins, 2009). In both methods subjects were randomized to treatment sequence decreasing the threat of order effects, increasing group equivalency in the cross-over design, minimizing variability in measurement due to subject or period differences, and increasing internal validity (Chow & Liu, 2014; Jones & Kenward, 2003). This study was well suited to single-subject repeated measures design, because children requiring an ACE procedure constitute a very small population with widely variable anatomic and physiologic causative factors making sample homogeneity difficult. The design allowed for frequency and volume adjustment of each flushing regimen as needed facilitating dose response comparison and aiding in identifying which flushing regimen required the minimal dose and administration frequency and had fewer side effects while achieving stool continence (Gast, 2010; Janosky et al., 2009; Kazdin, 2011). Subjects were limited to children who were scheduled for a cecostomy or appendicostomy ensuring a naïve gut to the effects of a flushing regimen and allowing for a true no-treatment baseline. Flush effects were reversible, making this intervention amenable to a withdrawal design. Specimen collection occurred after an active wash out period at the completion of each flushing regimen facilitating comparison of treatment effects on electrolytes and stool calprotectin, negating the possibility of carry-over effects.

Regulatory Considerations

The potential risks associated with this study conferred no greater than minimal risk as categorized by the National Institutes of Health (National Institutes of Health [NIH], 1998). However, it involved vulnerable subjects necessitating full Institutional Review Board (IRB) approval, legal guardian informed consent by at least one parent, and child assent for children age 7 and above (Knox & Burkhart, 2007; Pieper, 2008). In addition, although normal saline and USP glycerin have been used for over three decades in the clinical setting as ACE flushing solutions, administration of either solution through an ACE stoma is considered off-label use and therefore the study required FDA approval. Prior to submission to the IRB, the study design was reviewed by the Nemours Children's Clinic (NCC) Research Committee which made suggestions for revision but deferred to the investigator's Dissertation Committee for approval of study design and analysis. The UF IRB deferred to the NCC IRB because the study was to be completed at NCC. An IRB authorization agreement was completed, and the contract was signed by all parties. The proposal was submitted to the FDA and an IND was obtained. A Nemours Children's Clinic IRB application was completed. As a part of the NCC IRB application process, submissions for research involving investigational drugs and biologics and management of research pharmaceutical products were completed and approved. NCC IRB approval was obtained and renewed annually. Legal guardian informed consent and child assent for children 7 and above were obtained for each subject prior to the start of data collection.

Subjects

Subject characteristics' data were collected and included age in years and months, ethnicity, diagnosis, description of level of spinal cord lesion or anal-rectal malformation when appropriate, description of physical examination of anus, and the reason for undergoing an ACE procedure.

Setting

Following parental consent and child assent, baseline data were collected daily for a minimum of 2 weeks prior to surgery. Baseline data included the frequency of fecal soiling, and the frequency and severity of abdominal pain. Baseline blood sample for electrolytes and stool for calprotectin were obtained in the preoperative period. The baseline samples were collected prior to initiation of the preoperative bowel prep. Postoperatively, the child was randomly assigned to either start the saline or USP glycerin flush protocol. A clinician from the surgical division at NCC met with the parent and child in the immediate postoperative period for initiation of the first antegrade flush. At that time, the clinician reviewed the flush protocol in detail, including materials and procedures. The child received the first antegrade infusion during that hospital visit. A home visit was scheduled by the investigator for the initial antegrade flush following hospital discharge. Procedural reliability was ascertained by calculating procedural fidelity for each procedural variable to assure the intervention was accurately implemented in keeping with the methods section of the proposal. Procedural fidelity was ascertained prior to each regimen change during the clinic visit scheduled prior to each phase change.

Measures

Dependent variables collected at baseline were recorded daily and included the number of episodes of fecal soiling per day, the frequency and severity of abdominal pain measured using the Wong-Baker Faces Pain Rating Scale (WBFPRS) as the age-appropriate visual analog scale, serum electrolytes, and stool for calprotectin. The WBFPRS scale ranges from 0 (very happy without pain) to 10 (the worst pain imaginable). The WBFPRS has undergone extensive testing and has well established psychometrics in children (Tomlinson, von Baeyer, Stinson, & Sung, 2010; Wong & Baker, 1988).

Dependent variables collected postoperatively were obtained daily throughout all phases of the dosing and maintenance phases and included the number of episodes of fecal soiling per day, frequency and severity of abdominal pain and pain associated with antegrade flush administration measured using the WBFPRS as the age appropriate visual analog, and the presence of flush associated vagal symptoms. Serum electrolytes and stool for were calprotectin collected at the end of each dosing phase. Total flush volume was recorded with each flush and measured in mL. Direct parental observation with event recording was used to track and tally soiling episodes defined as non-toilet elimination. Dependent variables were measured and recorded by the parent using a data collection sheet specifically designed for this study. The parent was requested to call if the child was having accidents, discomfort greater than a 4 on the WBFPRS associated with the antegrade flush, or vagal symptoms. The investigator documented any event that could potentially cause a change in level, stability, or trend of the dependent variable not related to the intervention (i.e. initiation of antibiotics or an intercurrent illness).

Materials

Each child had a low-profile button in place to ease flush administration. A cabinet was identified in the clinic space for storage of the flushing solution with continuous temperature monitoring using a MCC

USB 501-LCD thermometer. The cabinet was locked with restricted key access. The temperature in the storage cabinet was consistently maintained between 15 and 30 degrees Centigrade. A temperature monitoring log was completed daily. No ambient temperature excursions occurred. Flush solution type, volume dispensed, lot numbers, and flush solution dispensing time and date were recorded in a dispensing log.

High Volume Flush

Each child had a low-profile button in place to ease flush administration. The normal saline was infused using a 1,000 mL enteral feeding bag with drip chamber and roller clamp hung from an IV pole or a hook on the bathroom wall located 5 feet above the toilet seat. Enteral feeding bag tubing and the low-profile device access tubing was primed with the high-volume flush prior to connecting the access tubing to the low-profile device and initiating the flush infusion. Step by step procedural directions were reviewed verbally with the parents and were reinforced through the provision of written instructions located in a parent notebook. The written procedure served as a check-off list to document procedural integrity which was checked during the initial home visit and each clinic visit scheduled with every change in flush solution and change in phase.

Low Volume Flush

Each child had a low-profile button in place to ease flush administration. For the low volume flush, room temperature USP glycerin was mixed with room temperature normal saline in a calibrated six-ounce plastic container with a screw top and subsequently poured into a 60 mL catheter-tipped syringe attached to the low-profile device access tubing. The tubing was primed and connected to the low-profile device. The syringe containing flush solution was held at the child's shoulder level while the flush solution infused. Following flush completion, the tubing and bag or syringe were washed in warm soapy water, thoroughly rinsed, and allowed to air dry. Step by step written procedural directions were included in a parent notebook and served both as procedural reinforcement and as a check-off list to document procedural integrity which was checked during the initial home visit and with each subsequent scheduled clinic visit completed with every change in flush solution and every change in phase.

Procedures

Randomization to one of the two treatment sequences occurred in the immediate postoperative period using restricted random assignment to force equal sample size and was accomplished using the SAS random number generator.

High Volume Regimen

The high-volume regimen consisted of normal saline flush at a starting dose of 10mL/kg infused every other day and adjusted by flush volume and frequency of administration until stability of target outcomes was achieved. Notification of any fecal soiling resulted in an additional 5 mL/kg volume adjustment with a subsequent increase in administration frequency, if needed, so as not to exceed a maximum dose of 500 mL administered daily for a child under five years of age and 1000 mL administered daily for a child over 5 years of age. If the child could not achieve continence on the maximum dose and had not been trialed on the alternate therapy, they were trialed on USP glycerin but did not proceed to the maintenance phase of the study. If the child experienced side effects greater

than 4 on the WBFPRS at the starting saline dose, flush volume was incrementally decreased as needed by 2.5 mL/kg to the lowest dose of 5 mL/kg. The goal of the dosing phase was to identify the lowest effective dose and flushing frequency that resulted in continence with minimal side effects. If the dose required to minimize side effects resulted in fecal soiling or the child had side effects greater than 4 on the WBFPRS at the lowest flush dose, and had not been trialed on the alternate therapy, they were trialed on USP glycerin but did not proceed to the maintenance phase of the study.

Low Volume Regimen

The low volume regimen consisted of USP glycerin diluted in normal saline instilled through the low-profile device starting on a dose of 20 mL of USP glycerin mixed in >20 mL of saline and adjusted by flush volume and frequency of administration until stability of target outcomes was achieved. The saline served as a diluent and was mixed at a sufficient dose to allow easy infusion of the solution through the ACE access tubing. Notification of any fecal soiling resulted in the addition of 5 to 10 mL with subsequent increase in frequency of administration, if needed, so as not to exceed 50 mL of USP glycerin administered daily. If the child could not achieve continence on the maximum dose and had not been trialed on the alternate therapy, they were trialed on high volume normal saline but did not proceed to the maintenance phase of the study. If the child experienced side effects greater than 4 on the WBFPRS at the starting USP glycerin dose, flush volume was incrementally decreased as needed by 5 mL increments to the lowest dose of 5 mL. The goal of the dosing phase was to identify the lowest effective dose and flushing frequency that resulted in continence with minimal side effects. If the dose required to minimize side effects resulted in fecal soiling or the child had side effects greater than 4 on the WBFPRS at the lowest flush dose, and had not been trialed on the alternate therapy, they were trialed on normal saline but did not proceed to the maintenance phase of the study.

Optimal Dose Regimen

Following optimal dose determination, the child was maintained on that volume and administration frequency for at least 2 weeks. A clinic visit was scheduled once the above criteria had been met. At that visit, the child was flushed at the optimal dose, labs were drawn, a stool sample collected, the procedure for the next regimen was reviewed with the parent and child, and procedural fidelity was ascertained.

Regimen Maintenance Phase

Following successful completion of the dose-response phase, patients were randomized for a second time to either a saline-glycerin-saline or a glycerin-saline-glycerin sequence. The maintenance phase of the study began by administering the established effective dose and frequency of administration for the first flush in the sequence. The child remained on treatment for 4 weeks. The treatment was withdrawn. The child was subsequently placed on the next treatment in the sequence at the pre-established effective dose and frequency for 4 weeks. The second flush was then withdrawn and the initial flush in the sequence was reintroduced for an additional two weeks. If the child experienced recurrence of fecal incontinence or discomfort greater than a 4 on the pain scale, they were dropped from the study. If they successfully completed the maintenance phase, the child was placed on the flushing regimen of his/her choice at the dose and frequency of administration that maintained continence.

Specimen Collection

A stool sample for calprotectin was obtained during the baseline phase prior to any pre-operative bowel prep and additional stool samples were obtained at the completion of each dosing phase for a total of 3 samples. Blood samples for electrolytes were drawn preoperatively and postoperatively at the end of each dosing phase at the time stool samples were obtained for a total of three samples. Funding was secured. Accounts were set up with an outside lab for processing blood samples for electrolyte determination and a second outside lab for processing stool samples for calprotectin.

Statistical Analysis

This study was a within subjects design with all subjects demonstrating consistent fecal incontinence at baseline and sufficient intervention and post-intervention data points to allow for time series analysis. Data points were graphed on an equal interval 2:3 ratio ordinate and abscissa scale line graph to prevent data distortion during visual analysis. Dependent measures were graphed on the ordinate scale with time-by-day graphed on the abscissa scale. Independent variable effects on target behaviors were analyzed using well established single-case methodology (Gast, 2010; Hartmann et al., 1980; Ma, 2006; Kazdin, 2011; Portney & Watkins, 2009). Clinicaltrials.gov is not configured to allow reporting outcomes from most methods of within subjects data analysis. Reported data was limited to the results from numeric descriptive and inferential analysis that could be adapted to the Clinicaltrials.gov format.

In addition to single-case analytic methodology, descriptive and inferential analysis was used to compare interventional effects and increase the reliability of visual methods analysis. Both the dosing and maintenance phase of the study constituted a 2-treatment crossover design with each child receiving both treatments in both interventional phases of the study (Portney & Watkins, 2009). Descriptive statistics included mean, median, range and standard deviation. A cross-over design compares two treatment sequences; therefore, the groups are independent (Chow & Liu, 2014). Of concern, carry over and direct-by-period interaction is a potential confound with cross-over designs, which if present, could bias treatment effects (Jones & Kenward, 2003; Senn, 2002; Shuster, 2007). The decision was made to use a two-tailed, two-sample pooled variance t-test to lend precision in the presence of carry over effects, and precision and accuracy in the presence of unequal sample size (Shuster, 2009). Significance level was set a priori at 0.05. Effect size was used to determine the magnitude of the treatment difference (Polit, 2010; Rempher & Silkman, 2007).

